Results: The median interval between HL and HF was 20.6 years. Fifty-seven percent of the cases had died at the end of follow-up, with a median time from HF to death of 3.6 years (interquartile range: 0.2-5.6 years). Mediastinal radiotherapy was applied through parallel-opposed fields. Average MHD for cases treated with RT was 25 Gy and for controls 22 Gy. Risk of HF increased in a non-linear way, with no increase at a MHD of 10 Gy, a 1.2-fold increased risk at a MHD of 20 Gy, and a 2.5-fold increased risk at a MHD of 30 Gy. Relatively low doses of anthracyclines (10-279 mg/m2) were associated with a 3.2-fold increased risk of developing HF (95%CI: 1.3-7.7) compared with patients who did not receive anthracyclines. High doses of anthracyclines (280-800 mg/m2) were associated with a similarly increased risk (RR: 2.8, 95%CI: 1.6-5.1). For patients who received anthracyclines in combination with mediastinal radiotherapy the risk of HF (RR: 2.90 at a MHD of 25 Gy) was slightly higher than the risk of mediastinal radiotherapy without anthracyclines (RR: 1.8 at a MHD of 25 Gy), although the difference was not statistically significant (p interaction=0.10). Classical risk factors for cardiovascular diseases did not confound or modify the association between treatment-related risk factors and HF risk.

Conclusion: Risk of HF increased non-linearly with mean heart dose in patients treated for HL. Our findings can be used to predict HF risk and may therefore be useful for patients and doctors both before treatment, during radiation treatment planning and in follow-up. Patients who received both anthracyclines and mediastinal radiation need to be followed carefully.

OC-0060

Cardiac risk prediction: Moving beyond a mean heart dose model?

M. Maraldo[1], F. Giusti[2], I. Vogelius[1], M. Lundemann[1], S. Bentzen[3], M. Van der Kaaij[4], B. Aleman[5], M. Henry-Amar[6], P. Meijnders[7], E. Moser[8], C. Fortpied[2], L. Specht[1]

[1]*Rigshospitalet, Department of Clinical Oncology, Copenhagen, Denmark*

[2]*European Organisation of Research and Treatment of Cancer, Department of Statistics, Brussels, Belgium*

[3]*University of Maryland School of Medicine, Department of Biostatistics, Baltimore, USA*

[4]*University Medical Centre Groningen, Department of Hematology, Groningen, The Netherlands*

[5]*Netherlands Cancer Institute, Department of Radiation Oncology, Amsterdam, The Netherlands*

[6]*Centre François Baclesse, Cancéropôle Nord-Ouest Data Processing Centre, Caen, France*

[7]*GZA/Iridium Cancer Network, Department of Radiation Oncology, Antwerp, Belgium*

[8]*Champalimaud Cancer Center, Department of Radiation Oncology, Lisbon, Portugal*

Purpose or Objective: Among 6039 patients with Hodgkin lymphoma enrolled in nine successive EORTC-GELA randomized trials (1964-2004), the effect of individual radiotherapy and chemotherapy doses on the risk of developing cardiac disease was investigated. We specifically analysed the added value from radiation dose-volume metrics on cardiac risk prediction as well as the impact of relapse treatment.

Material and Methods: For all patients, dose-volume metrics for the heart (mean dose, volume receiving 5 Gy (V5Gy), V10Gy, V20Gy, V30Gy, V40Gy) were retrospectively estimated by reconstructing individual treatments on representative computed tomography datasets. Cumulative doses of anthracyclines and vinca-alkaloids (mg/m2) were also obtained individually. Relapse occurring before a cardiac disease was analysed qualitatively (no, yes). Cardiac disease was reported during follow-up and through a patient-reported questionnaire (LSQ responders, 2009-2010 cross-sectional study). A multivariable Cox proportional hazards model with backwards selection was applied to test for patient- and treatment-related factors associated with cardiac disease. The resulting model was compared to a "mean heart dose"-model in terms of prognostic discrimination ability.

Results: 599 patients developed at least one cardiac disease event (465 events obtained from the 1919 LSQ responders). Significant predictors of cardiac disease were: cumulative dose of anthracyclines (HR=1.002 per 1 mg/m2 increase in cumulative dose; 95% CI, 1.001-1.003, p=0.005); (any) treatment given for a relapse (HR=1.286; 95% CI,1.001-1.65, p=0.049) and the radiation dose-volume metrics V30Gy (HR=1.007 per 1% increase in dose; 95% CI, 1.003-1.011, p=0.001) and V40Gy (HR=1.018 per 1% increase in dose; 95% CI,1.008-1.029, p<0.001). The freedom from cardiac disease estimates with the "V30Gy, V40Gy"-model are plotted against a "mean heart dose"-model (= mean heart dose, cumulative dose of anthracyclines, any relapse treatment) in figure 1.

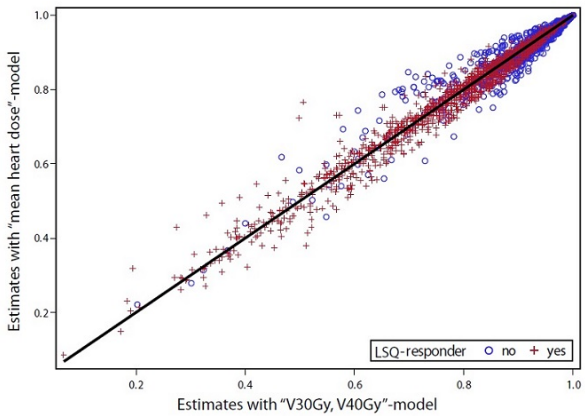


Figure 1: Freedom from cardiac disease estimates with the resulting "V30Gy, V40Gy"-model versus a "mean heart dose"-model.

Conclusion: In patients treated for Hodgkin lymphoma, the radiation dose-volume metrics V30Gy and V40 Gy, the cumulative dose of anthracyclines, and (any) treatment given for a relapse have a significant impact on the risk of subsequent cardiac disease. There seems to be no improved discrimination ability of the prognostic model when using radiation dose-volume metrics compared to the mean heart dose metric.

Proffered Papers: Brachytherapy 1: Prostate

OC-0061

Focal brachytherapy: what dose to what volume?

A. Haworth[1,2], H. Reynolds[1,2], M. DiFranco[3], Y. Sun[2], D. Wraith[4], S. Williams[2,5], B. Parameswaran[6], C. Mitchell[7], M. Ebert[8,9]

[1]*Peter MacCallum Cancer Centre, Physical Sciences, Melbourne, Australia*

[2]*University of Melbourne, Sir Peter MacCallum Department of Oncology, Melbourne, Australia*

[3]*Medical University of Vienna, Centre for Medical Physics and Biomedical Engineering, Vienna, Austria*

[4]*Queensland University of Technology, School of Public Health & Social Work, Brisbane, Australia*

[5]*Peter MacCallum Cancer Centre, Dept. Radiation Oncology, Melbourne, Australia*

[6]*Peter MacCallum Cancer Centre, Division of Radiation Oncology and Cancer Imaging, Melbourne, Australia*

[7]*Peter MacCallum Cancer Centre, Dept. Pathology, Melbourne, Australia*

[8]*University of Western Australia, Faculty of Science, Nedlands, Australia*

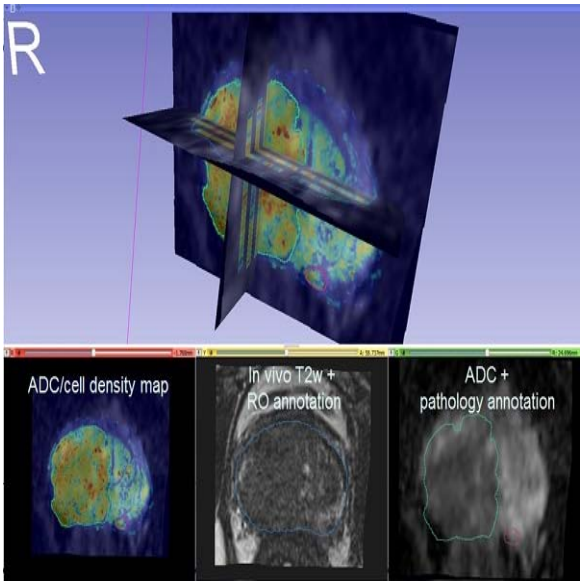
[9]*Sir Charles Gairdner Hospital, Dept Radiation Oncology, Nedlands, Australia*

Purpose or Objective: A novel approach to treatment planning for focal brachytherapy is described, utilizing a biologically-based inverse optimization algorithm and

biological imaging to target an ablative dose at known regions of significant tumour burden and a lower, therapeutic dose to low-risk regions. We describe our methods for defining target volume and prescription dose.

Material and Methods: To demonstrate how tumour characteristics may be extracted from multi-parametric MRI (mpMRI) to inform the previously validated biological model(1), 21 patients underwent in vivo mpMRI prior to radical prostatectomy. Co-registration of histology and imaging data using rigid and deformable registration was validated by matching feature points and annotated zonal regions. Automated methods for defining tumour location, tumour cell density (TCD) and Gleason Score (GS) in histology were developed to provide high resolution ground truth data(2,3). Similarly, using ground truth histology data, machine learning methods have been developed and tested to predict tumour location in mpMRI. Further developments are underway to predict TCD, GS and hypoxia in mpMRI to build a multi-level voxel map defining tumour location and characteristics to inform the biological treatment planning model.

Results: Co-registration of the in-vivo mpMRI with histology was achieved with an overall mean estimated error of 3.3 mm (Fig 1).



An ensemble-based supervised classification algorithm, trained on textural image features, demonstrates a highly sensitive method for automated tumour delineation in high resolution histology images(2). Colour deconvolution and the use of a radial symmetry transform provides measures of cell density, shown to highly correlate with an expert pathologist markup of tumour location(3). A Gaussian-kernel support vector machine demonstrated a tumour location predictive accuracy of >80% with potential for significant improvement using Bayesian methods to incorporate neighbourhood information. Similar statistical methods have demonstrated potential for mpMRI parameter/pharmacokinetic maps to be correlated with tumour characteristics including TCD, GS and hypoxia. Whilst imaging methods for hypoxia exist, providing reliable, high spatial resolution ground truth data remains challenging.

Conclusion: A novel approach to focal brachytherapy planning has been developed that incorporates mpMRI parameter/pharmacokinetic maps to inform a biological model and an inverse optimisation algorithm to maximise tumour control probability and minimise dose to organs at risk in prostate brachytherapy. The model can be equally applied to low and high dose rate brachytherapy, and possibly EBRT with high precision treatment delivery techniques. 1) Haworth, A. et al. Brachytherapy. 12, 628-36, (2013). 2) DiFranco, D. et al., Proc. SPIE 9420 (2015). 3) Reynolds, H. et al.. Proc. SPIE 90410S (2014).

OC-0062

High-dose-rate HDR boost for localized prostate cancer decreases long term rectum toxicity

S. Aluwini[1], M. Hoogeman[1], J. Lebesque[2], C. Bangma[3], L. Incrocci[1], W. Heemsbergen[2]
[1]*Erasmus MC Cancer Institute, Department of Radiation Oncology, Rotterdam, The Netherlands*
[2]*Netherlands Cancer Institute, Department of Radiation Oncology, Amsterdam, The Netherlands*
[3]*Erasmus MC Cancer Institute, Department of Urology, Rotterdam, The Netherlands*

Purpose or Objective: A High-Dose-Rate Brachytherapy (HDR-BT) boost combined with external beam radiotherapy (EBRT) produced excellent long term outcome and is an alternative for escalated EBRT (>72 Gy) for low and intermediate risk prostate cancer (PC) patients. The question remains whether the use of HDR-BT results in lower complication rates for equal tumour control. The aim of this study was to compare HDR-BT/EBRT combined to EBRT-only in terms of long-term patient-reported toxicity and oncological outcome for low and intermediate risk PC patients.

Material and Methods: Between 2000 and 2007 low and intermediate risk PC patients (n=231) were treated (stage T1b-T2a, G≤7, iPSA≤17) with a HDR-BT boost (3x6 Gy) combined with EBRT (25x1.8 Gy). Patients with a maximum prostate volume of 120 cc and a PSA, T-stage, and Gleason in the same range were selected (68 Gy: n=83, 78 Gy: n=74) from the Dutch randomized dose-escalation study (1997-2003). At least 1 follow-up questionnaire had to be completed. Genitourinary (GU) and gastrointestinal (GI) toxicity symptoms were prospectively assessed using same questionnaires in the period 1-7y years post-treatment. Prevalence of long term GU and GI symptoms were calculated with intervals of 1 year and compared between treatment groups (chi-square test). Biochemical failure free survival (BFFS) using the Phoenix definition (stratified for Gleason score) was calculated and compared (log-rank test).

Results: Median follow up was 8.8y for both 68 Gy and 78 Gy patients, and 6.8y for HDR-BT/EBRT. Median age was 69y and 68y, respectively. In general, post-treatment GU complaints were comparable between groups (dysuria, nocturia, day frequency, incontinence). Rectal blood loss was significantly lower for HDR-BT compared to 78 Gy, from the first year of follow-up and onwards ($p<0.001$). Rectal discomfort (pain/cramps) was significantly lower at 3y follow-up ($p<0.01$). Rectal incontinence showed lower rates as well, but these were not significant ($p=0.08$). Differences in stool frequency ≥ 4 were small and not significant. BFFS rates at 7y were 79%, 90%, and 96% (68 Gy, 78 Gy, HDR-BT) for Gleason <7 and 43%, 75%, and 91% for Gleason 7. BFFS was significantly higher in both the HDR-BT and 78 Gy group compared to 68 Gy ($p=<0.001$ and $p=0.034$ respectively), the difference between HDR-BT and 78 Gy was not significant ($p=0.11$).

Conclusion: HDR-BT/EBRT is associated with significantly lower long-term GI toxicity compared to escalated EBRT-only (78 Gy) with a favorably comparable 7 years tumor control.

OC-0063

Real-time in-vivo dosimetry in HDR prostate brachytherapy

J. Mason[1], B. Al-Qaisieh[1], A. Henry[2], P. Bownes[1]
[1]*St James Institute of Oncology, Department of Medical Physics, Leeds, United Kingdom*
[2]*St James Institute of Oncology, Clinical Oncology, Leeds, United Kingdom*

Purpose or Objective: Implement routine in-vivo dosimetry in HDR prostate brachytherapy and develop error detection thresholds for real-time treatment monitoring.